

## Effect of Sodium Nitroprusside on Ventilation-Perfusion Mismatching in Heart Failure

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Sodium nitroprusside has been shown to lower arterial partial pressure of oxygen ( $P_{aO_2}$ ) in patients with congestive heart failure and respiratory failure. The multiple inert gas elimination technique was used to evaluate the effect of sodium nitroprusside infusion on pulmonary gas exchange in five patients with congestive heart failure. During sodium nitroprusside infusion, mean values of cardiac output increased and mean values of arterial pressure, pulmonary artery pressure, pulmonary artery wedge pressure and pulmonary vascular resistance decreased. Cardiac output increased in each patient and  $P_{aO_2}$  decreased in all but one patient (mean  $75.6 \pm 15.1$  to  $68 \pm 17.5$  mm Hg,  $p = 0.032$ ).

Distributions of ventilation and perfusion showed increased perfusion of lung units with low ( $\leq 0.1$ ) ventilation-perfusion ratios in all subjects during sodium nitroprusside infusion (mean  $3.89 \pm 1.52$  to  $11.33 \pm 7.42\%$

of cardiac output,  $p = 0.027$ , paired  $t$  test). The amount of shunt (fractional perfusion of lung units with ventilation-perfusion ratio = 0) increased in the two patients with some shunt present in the baseline measurements. The mean total low ventilation-perfusion (shunt plus ventilation-perfusion  $\leq 0.1$ ) was significantly increased from  $4.38 \pm 1.54$  to  $14.7 \pm 9.37\%$  ( $p = 0.023$ ) during sodium nitroprusside infusion. Total low ventilation-perfusion perfusion was negatively correlated with mean pulmonary artery pressure and pulmonary artery wedge pressure ( $r = -0.949$  and  $-0.946$ , respectively).

Although sodium nitroprusside infusion increased cardiac output and overall oxygen transport in all patients, it worsened ventilation-perfusion mismatching. The mechanism is probably pulmonary vasodilation or increased cardiac output, or both.

Since 1929, sodium nitroprusside has been known to lower blood pressure (1), although it has been used to treat hypertension only since 1955 (2). Because no direct cardiac or nervous system effects have been demonstrated, it is thought to be a "pure" vasodilator. Because it lowers left ventricular afterload, it has also been widely used in recent years to treat left ventricular failure (3). Although sodium nitroprusside infusion results in increased cardiac output in patients with heart failure (4-6), it has also been shown to decrease arterial partial pressure of oxygen ( $P_{aO_2}$ ) in both human subjects (4-9) and animals (10-12), although most uniformly in patients with congestive heart failure and respiratory failure (9). The decrease in  $P_{aO_2}$  has been attributed to increased ventilation-perfusion inequality in the lung (4,6,7,13). However this has never been directly demonstrated to be the case in human subjects, and sodium nitro-

prusside might alter pulmonary gas exchange through other mechanisms.

To define how  $P_{aO_2}$  is determined by these multiple opposing factors requires a direct method of evaluating ventilation-perfusion mismatching, such as the multiple inert gas elimination technique by which one can estimate distributions of ventilation and perfusion as a function of ventilation-perfusion ratio (14) without using metabolized gases. Studies (12) utilizing the multiple inert gas elimination technique in dogs with and without oleic acid-induced pulmonary edema showed that only those with pulmonary edema had increased perfusion of lung units with low ventilation-perfusion ratios during infusion of sodium nitroprusside.

Ventilation-perfusion relations have not been studied in human subjects given sodium nitroprusside using the multiple inert gas elimination technique. Therefore, to determine the effect of sodium nitroprusside on ventilation-perfusion mismatching itself rather than just the well studied effect on  $P_{aO_2}$ , we used the multiple inert gas elimination technique to measure distributions of ventilation and perfusion before and during infusion of sodium nitroprusside in five patients with chronic congestive heart failure.

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## Methods

**Study patients.** We studied five men, each of whom had chronic congestive heart failure due to ischemic heart disease documented by prior acute myocardial infarction or cardiac catheterization and coronary arteriography, or both. Each patient was receiving digitalis and diuretic drugs. No medication was discontinued for this study. The men, whose ages ranged from 56 to 78 years, were all patients at the San Diego Veterans Administration Medical Center and each signed a consent form approved by the University of California-San Diego Committee on Investigations Involving Human Subjects. Each underwent right heart catheterization and short-term sodium nitroprusside infusion to evaluate his suitability for long-term oral vasodilator therapy.

**Methodology.** The patients were studied in the coronary care unit or cardiac catheterization laboratory. In each patient we placed percutaneously: 1) a peripheral intravenous cannula for infusion of a solution containing trace amounts of six inert gases for the multiple inert gas elimination technique; 2) a brachial or radial arterial cannula for blood sampling and monitoring of arterial pressure; and 3) a balloon-tipped flow-directed pulmonary artery catheter for sampling and measurement of pulmonary artery pressure and pulmonary artery wedge pressure. This catheter was equipped with a thermistor for measurement of cardiac output by the thermodilution technique.

**Measurements.** Intravascular pressures were measured with a Statham P23Db transducer coupled to appropriate amplifiers. The zero reference level was at the mid chest. Pressures reported in this study were electronically obtained mean values. Cardiac output by the thermodilution technique was calculated with a dedicated computer (American Edwards Laboratories model 9520A) after injection of 10 ml of room temperature 5% dextrose in water through the proximal port of the balloon-tipped catheter. Pulmonary vascular resistance ( $\text{dynes}\cdot\text{cm}^{-5}$ ) was calculated as  $(\text{Ppa} - \text{Ppaw}) \times 80 \div \text{CO}$ , where  $\text{Ppa}$  = mean pulmonary artery pressure,  $\text{Ppaw}$  = mean pulmonary artery wedge pressure and  $\text{CO}$  = cardiac output (liters/min). Three milliliter samples of arterial and pulmonary arterial blood were withdrawn slowly over 1 minute, placed in ice immediately and blood gases measured within 1 hour (813 pH/blood gas analyzer, Instrumentation Laboratory). In one patient (Case 3), pulmonary artery samples collected for measurement of blood gases during sodium nitroprusside infusion were clotted and the values were estimated from the ventilation-perfusion distributions (15).

*Oxygen consumption was calculated using the Fick principle:* oxygen consumption ( $\text{ml}/\text{min}$ ) =  $\text{CO} \times 10 \times (\text{arterial content} - \text{mixed venous content})$ , where oxygen contents are expressed as ml oxygen/100 ml blood. Total oxygen transport (ml of oxygen per minute) was calculated as:  $\text{O}_2 \text{ trans} = 10 \times \text{CO} \times \text{arterial O}_2 \text{ content}$ , where hemoglobin

concentration and saturation were calculated from the measured hematocrit ( $\text{hemoglobin} = \text{hematocrit} \div 3$ ) and blood gases, respectively, ( $\text{oxygen content} = 1.39 \times \text{hemoglobin} \times \text{percent oxygen saturation} \div 100$ ).

**Estimation of ventilation-perfusion distribution.** Ten milliliter samples of arterial and pulmonary artery blood were also collected for estimation of ventilation-perfusion distribution by the multiple inert gas elimination technique. Samples of mixed expired gas were collected by having the subject breath through a mouthpiece attached to a nonrebreathing valve connected to a heated mixing box. The patient was instructed to relax and avoid changes in respiratory pattern (tidal volume and frequency). Distributions of ventilation and perfusion were estimated from these samples as previously described (14). On the basis of the resulting distributions, we defined shunt as the fraction of total blood flow perfusing functional lung units with a ventilation-perfusion ratio equal to zero, blood flow in low ventilation-perfusion regions as the fraction of cardiac output perfusing lung units with ventilation-perfusion ratios of 0.1 or less and total low ventilation-perfusion unit perfusion as the sum of shunt and blood flow of low ventilation-perfusion units.

**Protocol.** Duplicate sets of blood and expired gas samples were collected in each patient under baseline conditions and during infusion of sodium nitroprusside. Pressures and cardiac output were measured immediately after collection of the samples. Before the samples were collected under each condition, the inert gas solution was infused for at least 30 minutes while the patient breathed through a mouthpiece and pulmonary artery pressure, arterial pressure and breathing pattern were stable.

**Sodium nitroprusside infusion.** After baseline samples had been collected, a fresh solution of sodium nitroprusside ( $100 \mu\text{g}/\text{ml}$ ) was infused by a constant rate infusion pump (IVAC Corporation). The rate of the infusion was adjusted to achieve a primary end point of reducing the pulmonary artery wedge pressure to 15 to 20 mm Hg, providing the mean arterial pressure did not decrease by more than 10 mm Hg. If the latter occurred and was tolerated well, this was taken as the end point of sodium nitroprusside infusion. Once these end points were reached, the infusion was maintained at constant rate for at least 20 minutes before samples were obtained. Infusion rates ranged from 0.5 to  $2.79 \mu\text{g}/\text{kg}$  per min. The sodium nitroprusside infusion was discontinued as soon as samples had been collected. No adverse effects were encountered in any of the patients.

**Statistical analysis.** Results obtained before and during sodium nitroprusside infusion were compared using one-tailed paired  $t$  tests since we had strong expectations that sodium nitroprusside would increase cardiac output, venous partial pressure of oxygen ( $\text{P}\bar{\text{v}}\text{O}_2$ ) and ventilation-perfusion mismatching, but would decrease pressures and  $\text{PaO}_2$ . Data shown in Table 1 for individual patients are the mean values

**Table 1.** Values Before and During Nitroprusside Infusion

Case	CO		Part		Ppa		Ppaw		PVR		PaO <sub>2</sub>		Pv̄O <sub>2</sub>		Shunt		Low VA/O		Total Low		O <sub>2</sub> Trans	
	B	D	B	D	B	D	B	D	B	D	B	D	B	D	B	D	B	D	B	D	B	D
1	3.3	3.8	80	78	33	25	21	14	291	232	59	50	33	29	0.55	4.5	5.9	22.1	6.5	26.6	630	652
2	3.2	4.2	66	60	34	31	22	19	299	226	82	83	29	34	0.0	0.0	4.8	15.9	4.8	15.9	613	791
3	2.4	6.6	63	56	32	28	23	20	298	97	70	53	25	36	1.9	12.5	2.7	8.0	4.6	20.5	443	1,140
4	3.8	4.2	80	69	52	40	35	24	357	305	99	89	30	35	0.0	0.0	3.9	4.45	3.9	4.45	634	693
5	2.8	5.0	83	72	48	45	34	24	394	335	69	66	29	33	0.0	0.0	2.2	6.25	2.2	6.25	467	750
Mean	3.1	4.8	74	67	40	34	27	20	327	239	76	68	29	33	0.49	2.9	3.9	11.3	4.4	14.7	557	805
± SD	0.52	1.1	9.2	8.9	9.4	8.4	6.9	4.1	45.8	92.1	15	17	2.3	2.7	0.82	4.6	1.5	7.42	1.5	9.37	94.1	195
p	0.04		0.01		0.01		0.01		0.02		0.03		0.04		0.12		0.03		0.02		0.06	

p values are derived from one-tailed paired *t* tests. B = before nitroprusside infusion; CO = cardiac output (liters/min); D = during nitroprusside infusion; Low VA/O = fractional perfusion of lung units with ventilation-perfusion ratio of 0.1 or less (%); O<sub>2</sub>Trans = total oxygen transport (ml of oxygen/min); Part, Ppa and Ppaw = systemic arterial, pulmonary artery and pulmonary artery wedge pressures, respectively (mm Hg); PaO<sub>2</sub> and Pv̄O<sub>2</sub> = arterial PO<sub>2</sub> and mixed venous PO<sub>2</sub>, respectively (mm Hg); PVR = pulmonary vascular resistance (dynes·s·cm<sup>-5</sup>); Shunt = fractional perfusion of lung units with ventilation-perfusion ratio equal to 0; Total low = shunt + Low VA/O (%).

(± standard deviation) of three measurements for cardiac output and the mean values of two measurements for PaO<sub>2</sub>, Pv̄O<sub>2</sub>, shunt, low ventilation-perfusion perfusion, total low ventilation-perfusion perfusion and total oxygen transport. Mean results were considered significantly different at the probability level of ≤ 0.05.

## Results

**Hemodynamic response.** Sodium nitroprusside infusion was associated with an increase in mean cardiac output from 3.12 ± 0.52 to 4.78 ± 1.12 liters/min (*p* = 0.040) and decreases in mean arterial pressure (from 74.4 ± 9.2 to 67.0 ± 8.9 mm Hg; *p* = 0.006), mean pulmonary artery pressure (from 40 ± 9.5 to 34 ± 8.4 mm Hg; *p* = 0.014), mean pulmonary artery wedge pressure (from 27 ± 6.9 to 20 ± 4.2 mm Hg; *p* = 0.008) and mean pulmonary vascular resistance (from 327 ± 45.8 to 239 ± 92.1 dynes·s·cm<sup>-5</sup>; *p* = 0.017). These mean changes were statistically significant and reflected changes seen in each individual patient.

**Blood gases.** PaO<sub>2</sub> decreased in all but one patient (Case 2), in whom it increased insignificantly from 82 to 82.5 mm Hg. Mean PaO<sub>2</sub> decreased from 75.6 ± 15.1 to 68.0 ± 17.5 mm Hg (*p* = 0.032). Mean Pv̄O<sub>2</sub> increased from 28.8 ± 2.3 to 33.4 ± 2.7 mm Hg (*p* = 0.045). Pv̄O<sub>2</sub> increased in all but one patient (Case 1). Oxygen consumption did not change significantly during sodium nitroprusside infusion (mean 221.7 ± 24.5 to 236.0 to 43.4 ml oxygen/min, *p* = 0.28).

**Ventilation-perfusion distribution.** Sodium nitroprusside infusion increased the amount of ventilation-perfusion mismatching. In all five patients, baseline distributions of ventilation and perfusion showed a distinct bimodal distribution with a small fraction (mean 3.89 ± 1.52%) of total blood flow in lung units associated with a low venti-

lation-perfusion ratio. Only two patients (Cases 1 and 3) had any shunt and these were very small (0.55 and 1.90%, respectively). During sodium nitroprusside infusion, the fraction of cardiac output perfusing lung units with a low ventilation-perfusion ratio increased in all five patients and substantially in three of these (Cases 1 to 3). The increase in mean low ventilation-perfusion perfusion (3.89 ± 1.52 to 11.33 ± 7.42%) was significant (*p* = 0.027). Shunt increased in the two patients (Cases 1 and 3) in whom it was present in baseline measurements (0.55 to 4.5% and 1.9 to 12.45%, respectively). No shunt developed in the remaining three patients. The increase in mean total low ventilation-perfusion perfusion (shunt + low ventilation-perfusion) was significant (4.38 ± 1.54 to 14.7 ± 9.37%, *p* = 0.023).

Patients 4 and 5 had a smaller increase in low ventilation-perfusion perfusion than did the other three patients (Table 1). These two patients were distinguished from the others by higher values for pulmonary artery pressure, pulmonary artery wedge pressure and pulmonary vascular resistance both in baseline measurements and during sodium nitroprusside infusion. Total low ventilation-perfusion perfusion during sodium nitroprusside infusion was negatively correlated (*r* = -0.9491 and -0.9462, respectively) with mean pulmonary artery pressure and mean pulmonary artery wedge pressure.

## Discussion

**Comparison with previous studies.** Several studies have shown that sodium nitroprusside infusion leads to lower arterial partial pressure of oxygen (PaO<sub>2</sub>) in human subjects with heart failure (4-6) and respiratory failure (9). In anesthetized normal subjects, the reported results (7,8,16-18) are conflicting, suggesting a variable effect. Almost all studies (5,12,19-25) in normal animals have failed to demon-

strate this decrease in  $\text{PaO}_2$ . Mechanisms other than ventilation-perfusion mismatching that might change  $\text{PaO}_2$  include: 1) increased cardiac output leading to increased mixed venous  $\text{PO}_2$  ( $\text{P}\bar{\text{V}}\text{O}_2$ ) and, thus, to increased  $\text{PaO}_2$  if a fixed amount of ventilation-perfusion mismatching is present; and 2) changes in tissue perfusion leading to changed oxygen consumption. The only previous study (12) of sodium nitroprusside that used the multiple inert gas elimination technique in dogs demonstrated that dogs studied after oleic acid-induced pulmonary edema developed decreased  $\text{PaO}_2$  and increased shunt and perfusion of lung units with low ventilation-perfusion ratio during infusion of sodium nitroprusside.  $\text{PaO}_2$  and ventilation-perfusion matching were not significantly changed in normal dogs.

*In all five of our patients with left ventricular failure*, we found that infusion of sodium nitroprusside is associated with increased ventilation-perfusion mismatching in the lung, namely, increased perfusion of functional lung units with ventilation-perfusion ratios of 0.1 or less. This change was associated with a decrease in  $\text{PaO}_2$  in all but one patient. The small amount of perfusion of lung units with low ventilation-perfusion ratio found in the baseline samples was probably secondary to mild pulmonary edema.

**Possible mechanisms of nitroprusside effect.** Decreased pulmonary vascular resistance during infusion of sodium nitroprusside in human subjects has been reported in patients with congestive heart failure and adult respiratory distress syndrome and a group of nine normal subjects (4,5,6,9) although it was not significantly decreased in five patients with chronic obstructive pulmonary disease (8), patients with spontaneous hypertension after coronary artery bypass surgery (1) and patients after acute myocardial infarction (26). Results of animal studies (11,12,25,27,28) have been inconsistent. We also noted decreased pulmonary vascular resistance, which suggests that sodium nitroprusside had a pulmonary vasodilator effect, although this change is difficult to interpret in the setting of increased cardiac output. Moreover, previous work (12,22,28-30) has produced strong evidence indicating that sodium nitroprusside prevents hypoxic pulmonary vasoconstriction.

*Thus, vasodilation (or increased perfusion through indirect mechanisms) occurs largely in underventilated areas*, accounting for the increased perfusion of lung units with low ventilation-perfusion ratio. This concept is supported by our observation that the two patients (Cases 4 and 5) with the least increase in perfusion of units with low ventilation-perfusion ratio were those with the least decrease in pulmonary vascular resistance during sodium nitroprusside infusion. These patients had higher baseline values of pulmonary artery pressure and pulmonary vascular resistance and more "fixed" pulmonary vasculature indicated by less decrease in pulmonary vascular resistance during sodium nitroprusside infusion.

*However, we also observed significant increases in cardiac output during sodium nitroprusside infusion.* An increase in cardiac output alone has been shown in dogs to increase fractional perfusion of lung units with low ventilation-perfusion ratio in the presence of a bimodal ventilation-perfusion distribution in an asthma model (H. Bencowitz, unpublished results). It has also been shown (31,32) to increase shunt fraction in oleic acid-induced pulmonary edema. However, the effect of changes in cardiac output on  $\text{PaO}_2$  is more complicated, because increased  $\text{P}\bar{\text{V}}\text{O}_2$  increases cardiac output and leads to increased  $\text{PaO}_2$  for any given amount of ventilation-perfusion mismatching. Thus, the net effect of cardiac output on  $\text{PaO}_2$  is the balance between two opposing events: increased  $\text{P}\bar{\text{V}}\text{O}_2$  and worsened ventilation-perfusion matching. Therefore, a change in  $\text{PaO}_2$  can not be used to infer the effect on ventilation-perfusion relations. This is illustrated by Case 2 in which  $\text{PaO}_2$  remained essentially unchanged during sodium nitroprusside infusion, although the perfusion of lung units with low ventilation-perfusion ratio increased substantially. If the cardiac output had not increased,  $\text{PaO}_2$  would have been lower.

**Clinical implications.** Although infusion of sodium nitroprusside in our patients had a beneficial effect on cardiac output and overall oxygen transport, it adversely altered the relation between ventilation and perfusion in the lung. Moreover, many patients in whom sodium nitroprusside therapy is indicated are hypoxic and it has been shown that sodium nitroprusside is more detrimental to gas exchange in patients with heart failure and adult respiratory distress syndrome than in normal subjects. Therefore, when sodium nitroprusside is used or the dosage increased in patients with heart failure, one should be aware of its potentially deleterious effects.

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